TOXICOLOGY

The Agency's assessment of diisocyanate toxicity supports the need for exposure reductions. Diisocyanates are extremely reactive. Although they may affect many organ systems, the primary target of toxicity is the upper and lower respiratory tract. In addition, diisocyanates are known dermal sensitizers and, some are respiratory sensitizers. The following is a summary of the data derived from animal and epidemiological studies or case reports in humans.

For repeated dose studies, only information from inhalation studies have been included. Studies conducted by the oral route are not considered to be relevant because the oral route is not expected to be an occupational route of exposure nor are releases to water expected to result in exposures to diisocyanates because the diisocyanate moiety will hydrolyze in water.

Developmental and reproductive toxicity studies are not included in this profile because they are not the most sensitive endpoints for this class of compounds.

Repeated Dose Respiratory Tract Toxicity

Based on repeated dose studies (14-90 day) in animals by the inhalation route, both aromatic and aliphatic diisocyanates appear to be of high concern for pulmonary toxicity at low exposure levels. Inflammation of the lungs and nasal cavities as well as histopathological changes that included squamous metaplasia in the nasal passages, and submucosal infiltration of mononuclear cells, goblet cell hyperplasia and erosion of respiratory epithelium and bronchus-associated lymphatic tissue in the lungs were observed in animal studies at doses of less than 5 mg/m^3 (<1 mg/kg). Based upon a very limited data set, it appears that diisocyanate prepolymers exhibit the same respiratory tract effects in repeated dose studies, but a slightly higher doses. In addition, also based upon a very limited data set, it appears that diisocyanate polymers induce the same effects in repeated dose studies as the monomers, at similar doses. This may be in part due to the high percent of monomer (>40%) in the polymer formations.

There is also evidence that both aromatic and aliphatic diisocyanates are acutely toxic via the inhalation route.

Oncogenicity

Most members of the diisocyanate category have not been tested for carinogenic potential. Commercially available Poly-MDI was tested in a 2-year inhalation study in rats. The tested material contained 47% aromatic 4,4'-methylenediphenyl diisocyanate (MDI) and 53% higher molecular weight oligomers. Interim sacrifices at one year showed that males and females in the highest dose group (6 mg/m^3) had treatment related histological changes in the nasal cavity, lungs and mediastinal lymph nodes. The incidence and severity of degeneration and basal cell hyperplasia of the olfactory epithelium and Bowman's gland hyperplasia were increased in males at the mid and high doses and

in females at the high dose following the two year exposure period. Pulmonary adenomas were found in 6 males and 2 females, and pulmonary adenocarcinoma in one male in the high dose group. However, aliphatic hexamethylene diisocyanate (HDI) was found not to be carcinogenic in a two year repeated dose study in rats by the inhalation route. HDI has not been tested in mice by the inhalation route.

Through the oral route is not an expected route of exposure to humans, it should be noted that in two year repeated dose studies by the oral route, aromatic toluene diisocyanate (TDI) and 3,3'-dimethoxy-benzidine-4,4'-diisocyanate (dianisidine diisocyanate, DADI) were found to be carcinogenic in rodents. TDI induced a statistically significant increase in the incidence of liver tumors in rats and mice as well as dose-related hemangiosarcomas of the circulatory system and has been classified by the Agency as a B2 carcinogen. DADI was found to be carcinogenic in rats, but not in mice, with a statistically increase in the incidence of pancreatic tumors observed.

Respiratory and Dermal Sensitization

Based on the available toxicity data in animals and epidemiologic studies of humans, aromatic diisocyanates such as TDI and MDI are strong respiratory sensitizers. Aliphatic diisocyanates are generally not active in animal models for respiratory sensitization. However, HDI and possibly isophorone diisocyanate (IPDI), are reported to be associated with respiratory sensitization in humans. Symptoms resulting from occupational exposure to HDI include shortness of breath, increased bronchoconstriction reaction to histamine challenges, asthmatic reactions, wheezing and coughing. Hazardous Substance Database (HSDB, 1995) cites two case reports of human exposure to IPDI by inhalation that suggest IPDI is a respiratory sensitizer in humans. In view of the information from case reports in humans, it would be prudent at this time to assume that both aromatic and aliphatic diisocyanates are respiratory sensitizers. Studies in both human and mice using TDI, HDI, MDI and dicyclohexylmethane-4,4'-diisocyanate (HMDI) suggest cross-reactivity with the other diisocyanates, irrespective of whether the challenge compound was an aliphatic or aromatic diisocyanate.

At present, there appears to be no reliable animal model for testing for respiratory sensitization that gives an adequate correlation with human respiratory sensitization. In the absence of such a model, and in light of the conflicting animal and human data, it is prudent to assume that all diisocyanates have the potential to be human respiratory sensitizers.

Diisocyanates are moderate to strong dermal sensitizers in animal studies. There seems to be little or no difference in the level of reactivity between aromatic and aliphatic diisocyanates.

Dermal Irritation

Skin irritation studies performed on rabbits and guinea pigs indicate no difference in the effects of aromatic versus aliphatic diisocyanates. The level of irritation ranged from slightly to

severely irritating to the skin. One chemical, hydrogenated MDI (1,1'-methylenebis-4-isocyanatocyclohexane), was found to be corrosive to the skin in guinea pigs.

Conclusions

In general, there apepars to be little or no difference between aromatic and aliphatic diisocyanates for the above listed end-points. In addition, there are insufficient data available to make any major distinctions between polymeric and monomeric diisocyanates. Based on repeated dose studies in animals by the inhalation route, both aromatic and aliphatic diisocyanates appear to be of high concern for pulmonary toxicity at low exposure levels. Based upon a very limited data set, it appears that diisocyanate polymers exhibit the same respiratory tract effects as the monomers in repeated dose studies at similar doses. However, the polymers are known to have a high percentage of monomer in them. There is also evidence that both aromatic and aliphatic diisocyanates are acutely toxic via the inhalation route. Most members of the diisocyanate category have not been tested for carcinogenic potential. Though the aromatic diisocyanates tested positive and the one aliphatic diisocyanate tested negative in one species, it is premature to make any generalizations about the carcinogenic potential of aromatic versus aliphatic diisocyanates. In the absence of more human data, it would be prudent at this time to assume that both aromatic and aliphatic diisocyanates are respiratory sensitizers. Diisocyanates are moderate to strong dermal sensitizers in animal studies. Skin irritation studies performed on rabbits and guinea pigs indicate no difference in the effects of aromatic versus aliphatic diisocyanates.

See the New Chemicals Program's Category description for Isocyanate Compounds in Appendix A**.**

APPENDIX A

ISOCYANATE CHEMICAL CATEGORY

Category: Diisocyanates Human Health

Definition. Any molecular structure containing two or more isocyanate groups is considered to be a member of the category for new chemical purposes:

$$R\text{-}(N{=}C{=}O)_{\geq 2}$$

Members of the class include new isocyanate monomers as well as new oligomers, polymers, prepolymers, or reaction products of existing isocyanate monomers. Most new chemical diisocyanates of concern are polymers or oligomers containing well-known diisocyanate monomers such as toluene diisocyanate (TDI) or 4,4'-methylenediphenyl diisocyanate (MDI).

Hazard Concerns. Diisocyanates are of concern for potential dermal and respiratory sensitization, and for pulmonary toxicity. Based on conflicting animal and human data for respiratory sensitization, the Agency has determined that there is presently not a reliable animal model for testing diisocyanates for potential respiratory sensitization. At this time, it is assumed that all diisocyanates may be potential human respiratory sensitizers.

Most members of the diisocyanate category have not been tested for carcinogenic potential. Though the aromatic diisocyanates [MDI, TDI, dianisidine diisocyanate (DADI)] tested positive and one aliphatic diisocyanate [hexamethylene diisocyanate (HDI)] tested negative in one species, it is premature to make any generalizations about the carcinogenic potential of aromatic versus aliphatic diisocyanates.

Boundaries. Structures with an isocyanate equivalent weight of $\geq$5,000 are presumed not to pose a hazard under any conditions. Typically, concerns are confined to those species with molecular weights <1,000.

Frequently, new chemical isocyanates are manufactured with a significant excess of isocyanate monomer. Under these circumstances, the excess monomer is usually regarded as more hazardous than the "new" chemical component, and these PMN substances are ordinarily not regulated under §5 of TSCA. For the purposes of risk assessment within the New Chemicals Program, a PMN substance is considered "existing" if more than 50% of the free isocyanate groups in the PMN substance (new chemical component + existing chemical monomer) reside on unreacted monomer(s). This does not relieve a Company, however, of any obligations to submit a PMN for the new chemical isocyanate if indeed it is not listed on the TSCA Inventory.

General Testing Strategy. The following testing is recommended to address the potential for pulmonary toxicity and dermal sensitization.

1. Dermal sensitization (OPPTS 870.2600).

2. 90-day Subchronic inhalation toxicity test in rodents (OPPTS 870.3465).

In addition, appropriate hazard communication needs to be developed and implemented.

Health and Safety Information. The following information provides guidance in developing hazard communication and protective measures language to accompany new diisocyanate chemicals and formulations. It is based on the Agency's current understanding of the hazards associated with diisocyanates and the most effective means to limit exposure.

> **Warnings**. Exposure to diisocyanates may cause the following human health effects: skin irritation and allergic reactions, respiratory irritation, respiratory sensitization, and lung toxicity; some diisocyanates also may cause cancer. The likelihood that these effects will occur depends on a number of factors; among them, the level of exposure, frequency of exposure, part of the body exposed, and sensitivity of the exposed individual.

Symptoms of allergic reaction and respiratory sensitization include rashes, cough, shortness of breath, asthma, chest tightness and other breathing difficulties. There is uncertainty as to the mechanism by which sensitization occurs. In sensitized individuals, exposure to even small amounts of diisocyanates (below government-recommended workplace exposure levels) may cause allergic respiratory reactions like asthma and severe breathing difficulties. <u>It is especially important to note that contact with skin may lead to respiratory sensitization or cause other allergic reactions</u>. In some cases, the effects of diisocyanate exposure may be immediate and life-threatening; in others, the effects may be delayed and occur hours after the exposure has ended. Repeat or prolonged exposure to diisocyanates may also cause irritation to eyes, skin, respiratory tract and lungs, as well as adverse chronic lung effects, like decreased lung capacity and function. Individuals experiencing shortness of breath, tightness in the chest or other problems breathing should seek immediate medical attention.

> **Protective Measures.** In workplaces where individuals handle diisocyanates or coatings or other formulations that contain them, an industrial hygiene and safety program should be operative. Important components of this program include: hazard communication and training on safe handling practices; use of efficient and well-maintained application equipment, engineering controls and personal protective equipment; housekeeping procedures including spill prevention and cleanup practices; and, if feasible, means to measure airborne levels of polyisocyanates and diisocyanates.

During spray applications, workers should take precautions to avoid breathing vapors, mists or aerosols. Inhalation exposures should be limited to <0.05 mg/m^3 as an 8-hour time-weighted average (TWA) for combined polyisocyanates and diisocyanates.[2] Engineering controls should serve as the first, most effective means of reducing airborne polyisocyanate and diisocyanate concentrations; an appropriate NIOSH/MSHA-approved respirator should be used as a secondary tool to lower exposures. Currently, downdraft spray booths and high-volume low-pressure (HVLP) spray guns appear to offer the most efficient technology to reduce inhalation exposures; a maintenance program should always be used to ensure optimal operating efficiencies. To limit dermal contact, individuals should wear impermeable gloves, protective clothing and goggles or glasses with side shields.

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[2]0.05 mg/m^3 or 0.005 ppm TWA is the American Conference of Government Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) for each hexamethylene diisocyanate (HMDI), toluene-2,4-diisocyanate (TDI), and methylene bisphenyl isocyanate (MDI). Also, OSHA has set 0.02 ppm as exposure ceilings for both TDI and MDI.